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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,153	03/01/2004	Andreas Hirsch	4451.003300	9981

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EXAMINER	
SAMALA, JAGADISHWAR RAO	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,153	HIRSCH ET AL.	
	Examiner	Art Unit	
	Jagadishwar R. Samala	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *10-14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/21/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

Receipt of the response to Restriction requirement and Applicant's arguments/remarks filed on 11/28/2006 is acknowledged.

Election was made **without traverse** and election is made **Final**.

Claims 1-16 are pending. Claims 1-9 and 15-16 are withdrawn and claims 10-14 are examined.

Claims 10-14 are rejected.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention wherein the amphiphilic fullerene comprising a functional group as tissue-recognition moieties. Because there is no clear description and/or envision in specifications to tissue-recognition moieties. The state of art would not recognize the instant claim 11 and further more there is no screening or essay method to find an appropriate/suitable

compound capable to assist in the achievement of a desired tissue-recognition moieties in a patient as a therapeutic function.

Since applicant fails to provide any guidance as to how effects the processes claimed. A general recitation in the specification that the amphiphilic fullerene comprising a functional group selected from the group consisting of tissue-recognition moieties is insufficient.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 10-12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Klibanov et al. (US 6,245,318 B1 here after '318) or Watson et al. (US 5,688,486 here after '486)

With respect to claim 10, the reference '318 discloses an ultrasound contrast agent comprising a monolayer microbubble-shell and a composition of the general formula A-P-L, wherein A is an ultrasound contrast agent microbubble-shell binding moiety; P is a spacer arm; and L is a ligand. (see column 1, lines 55-62). The ultrasound contrast agent include lipids, phospholipids, long-chain aliphatic hydrocarbon

derivatives, lipid multichain derivatives, comb-shaped lipid-polymer derivatives, steroids, fullerenes, polyaminoacids, and thereof (see column 2, lines 55+) Spacer arms include a branched or linear synthetic polymer or a biopolymer like PEG, PVP, polyvinyl alcohol and starch. The lipid-PEG ligand compounds used for the attachment of ligands to liposomes (bilayer of lipids), wherein in liposomes, the lipid bilayer is formed with the lipid residues facing each other, in the monolayer-coated gas bubble (see column 2, lines 28-42).

With respect to claim 11, the reference '318 discloses the ligands designed to bind specifically to receptors for angiogenesis factors expressed in tumor microvasculature and coupled to echogenic contrast agents enhance the specificity and sensitivity of ultrasound agents detection(see column 3, lines 33-39). Biotinylated phosphatidylethanolamine is incorporated into the liposome membrane, than avidin is added and attached to biotin on liposomes (see column 5, lines 27-30). Although tissue recognition moiety as required by the instant claim as not been explicitly mentioned, because the binding activity to receptors assist in the achievement of desired tissue-recognition and the claim is met by the teaching of the cited reference.

With respect to claim 12, the reference '318 discloses the administering of diagnostic compositions, either systemically or locally to the organ or tissue to be imaged and the patient then subjected to the imaging procedure (C-scan). Such doses may vary widely, depending upon the particular agent employed, the organs or tissues, which are the subject of the imagaing procedures (see column 6, lines 50+).

With respect to claim 14, wherein the amphifullrene liposome is aerosolized. The aerosolized liposome is an alternate dosage form of the therapeutic agent. This is a minor variation comprising combinations of gas and liquid active ingredients. Klibanavo discloses the ultrasound imaging agents are capable of being gas filled, liquid filled or combination of gas and liquid suitable for use as aerogels, include decafluorobutane, decafluoroisobutane, octafluoropropane and thereof (see column 4, lines 5-15). Thus, the claim is readily envisaged by the teaching of the cited reference and the claim is properly included in the rejection.

5. Claims 10-12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Watson et al. (US 5,688,486 here after '486)

Claims 10,12 and 14 are drawn to a amphiphilic fullerene liposome, comprising: a amphiphilic fullrerene, and a therapeutic agent located on the surface of the liposome, wherein the therapeutic agent is a CT contrast agent and is a sedating drug.

With respect to claims 10,12 and 14, the reference '486 discloses the use of macromolecular compounds having tight molecular meshes, for e.g., non-diamond carbon allotropes and in particular carbon based macromolecular structures such as fullerences, graphite and amorphous carbons, as therapeutic or diagnostic agents, in particular as contrast enhancing agents in imaging modalities such as MRI, ultrasound, PET, Overhauser MRI, scintigraphy, X-ray CT, SPECT, magnetometric tomography, EIT, visible and ir imaging and as carriers for signal reporters. Contrast agents may be administered in medical imaging procedures to enhance the image contrast in images of

a subject to be more clearly observed or identified, generally for different organs, tissue types or body compartments (see column 1, lines 7-25).

Watson also discloses a diagnostic or therapeutic entity is to be carried by the mesh structure is achieved in at least four ways: skeleton atoms in the mesh structure (carbon atoms in a carbon allotrope) may be derivatised to bind the diagnostic or therapeutic entity directly or indirectly to the skeleton; diagnostically or theraperutically effective atoms may be substituted for framework atoms; the diagnostic or therapeutic entity may intercalated between adjacent webs (e.g. in graphite, a buckytube or an amorphous carbon); or the diagnostic or therapeutic entity may be entrapped within a cage-like mesh (e.g. within a buckyball). In each case the skeleton may be derivatized to enhance other properties of the macromolecule, e.g. to include hydrophilic or lipophilic groups or biologically targeting groups or structures. Examples of macromolecules, biomolecules and macro-structures include polymers, dendrimers, polysaccharides, proteins, antibodies, glycoproteins, proteoglycans, liposomes, aerogels, and thereof to assist in the achievement of a desired biodistribution (see column 3, lines 61+ and column 4, lines 1-29).

As to claim 11 which require tissue recognition moieties (elected species), Watson teaches various compounds such as the conjugation of fullerenes to saccharides offers an attractive rout to achieving desired biodistribution for the macromolecular cages. Similarly the conjugation of fullerenes to biotargetting proteins e.g. asialoglycoprotein to increase their solubility and/or biotolerabbility (see column 7,

lines 1-5). Because there is no specific teaching about what and how tissue-recognition moiety is or can be screened, one skilled artisan would readily envisaged the said protein would be capable of recognizing different tissues because of interactions between receptors (made out of proteins as well) as recognized by general molecular chemistry, thus the claim is met by the teaching of the cited reference. Although tissue recognition moiety as required by the instant claim as not been explicitly mentioned, because the binding activity to receptors assist in the achievement of desired tissue-recognition and the claim is met by the teaching of the cited reference.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klibanov et al. US 6,245,318 B1 (Klibanov) in view of Ostensen et al. US 6,375,931 (Ostensen)

The patent '318 discloses an ultrasound contrast agent comprising a microbubble-shell and a composition of the general formula A-P-L where A is an ultrasound contrast agent microbubble-shell binding moiety (fullerene); P is a spacer arm include a branched or linear synthetic polymer or a biopolymer like lipid-PEG-ligand compounds for the attachment of ligands to liposomes (bilayers of lipids) and L

is a ligand which include biomolecule to enhance tissue targeting through specificity and delivery of therapeutic agent (see column 1, lines 55+).

Klibanov fails to disclose sedating agent wherein additional therapeutic agent is included therein. However, the use of sedative agents for local anesthetics is well known in the art as shown by Ostensen.

Ostensen discloses preparations comprising fullerene C60 (see column 28, lines 27-30 and column 33, lines 59-60) that may be employed as delivery agents for bioactive moieties such as therapeutic drugs like sedative agents (e.g. amobarbital,ethinamate, bupivacaine, etidocaine and droperidol thereof) because addition of sedating/anesthetic agent provide the advantage of delivery agents for bioacative moieties such as therapeutic drugs (i.e. agents having a beneficial effect on a specific disease in a living human or non-human animal), particularly to targeted sites (see column 18, lines 9-20).

It would have been obvious to one of ordinary skill in the art to modify the therapeutic agent disclosed by Klibanov to include a sedating drug as an additional therapeutic agent because Ostensen teaches that sedating/anesthetic agent are useful as potential adjuvants as local anesthetic/general anesthetic agents because they provide the advantage of the therapeutic agents to targeting tissue through specificity and delivery. One of ordinary skill in the art would have been motivated to include the sedating drug as an additional therapeutic agent in the ligand, linked to liposome composition disclosed by Klibanov because the sedating/anesthetic agent taught by Ostensen, while having a similar effect as a therapeutic agent, provides an additional

and separate advantage as compared to the therapeutic agent disclosed by Klibanov. Also, it would have been obvious to one of ordinary skill in the art to include the sedating drug as vehicles for therapeutically active agent for contrast-enhancing moieties for imaging modalities other than ultrasound, for e.g. X-ray, light imaging, magnetic resonance and scintigraphic imaging agents, because it is well known in the art that such image contrast-enhancing agents including the sedating drug can be practicalized to improve the method of diagnosing or treating patients using improved therapeutic agents as shown by Ostensen.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 10-14 are rejected on the ground of nonstatutory obviousness type double patenting as being unpatentable over claim 1-12 of US Pat. 7,070,810 B2. Although the conflicting claim is not identical, they are not patentably distinct from each other because claims of the instant application are drawn to a amphifullerene liposome, comprising: an amphiphilic fullerene and a therapeutic agent located on the surface of the liposome, between layers of the liposome, entrapped within the liposome, or associated with fullerene while the claim of the US Pat. Application is a vesicle having an interior, an exterior, and a wall, wherein the wall comprises one or more layers, wherein each layer comprises a substituted fullerene and method of administering a therapeutic agent present in (a) the interior of a vesicle having an interior, an exterior, and a wall (b) a portion of the wall between two layers, or (c) both, to the mammal, wherein the wall comprises one or more layers, wherein each layer comprises a

substituted fullerene. Both require fullerene, liposomes and therapeutic agent. Thus, the instant claims are directly within the scope of the claims of the US Pat. Application. As to claim 12, the US Pat. 7,070,810, overlapping the scope with instant claim because, the patent "810 includes radiotherapeutic agent in light of specification (see column 12, lines 23). Thus scope is overlapping each other and properly included in the rejection because they are patentably distinct from each other. As to claim 14, wherein the amphifullrene liposome is aerosolized. The aerosolized liposome is an alternate dosage form of the therapeutic agent. This is a minor variation comprising combinations of gas and liquid active ingredients. It is well known in the art that, the ultrasound imaging agents are capable of being gas filled, liquid filled or combination of gas and liquid suitable for use as aerogels. Thus, the claim is readily envisaged by the teaching of the prior art and the claim is properly included in the rejection.

Conclusion

1. At present no claims are allowed.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jagadishwar R. Samala whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jagadishwar R Samala
Examiner
Art Unit 1618

sjr

VICKIE KIM
PRIMARY EXAMINER